**Antiviral drugs**

Antiviral drugs are a class of [medication](http://en.wikipedia.org/wiki/Medication) used specifically for treating [viral](http://en.wikipedia.org/wiki/Virus) [infections](http://en.wikipedia.org/wiki/Infection). Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development. Viruses are obligate intracellular parasite, lack cell wall, cell membrane and metabolic process, so it depends on host metabolic process.

**Virus life cycle**

 Viral life cycles vary in their precise details depending on the species of virus, but they all share a general pattern:

* **Attachment to a host cell.**
* **Release of viral genes and possibly enzymes into the host cell.**
* **Replication of viral components using host-cell machinery.**
* **Assembly of viral components into complete viral particles.**
* **Release of viral particles to infect new host cells.**

**Anti-viral targeting**

**Before cell entry**

This stage of viral replication can be inhibited in two ways:

1. Anti-receptor antibodies

2. anti-VAP [antibodies](http://en.wikipedia.org/wiki/Antibody), receptor anti-idiotypic antibodies.

**Entry inhibitor**

A number of "entry-inhibiting" or "entry-blocking" drugs are being developed to fight HIV.

**Uncoating inhibitor**

[Amantadine](http://en.wikipedia.org/wiki/Amantadine) and [rimantadine](http://en.wikipedia.org/wiki/Rimantadine%22%20%5Co%20%22Rimantadine), have been introduced to combat influenza. These agents act on penetration/uncoating. [Pleconaril](http://en.wikipedia.org/wiki/Pleconaril) works against [rhinoviruses](http://en.wikipedia.org/wiki/Rhinovirus).

**Viral synthesis inhibitors**

1. **Reverse transcription inhibitors**

This approach is more commonly associated with the inhibition of [reverse transcriptase](http://en.wikipedia.org/wiki/Reverse_transcriptase) (RNA to DNA) than with "normal" transcriptase (DNA to RNA).[zidovudine](http://en.wikipedia.org/wiki/Zidovudine%22%20%5Co%20%22Zidovudine) (AZT).

1. **Integrase** **inhibitors** Another target is [integrase](http://en.wikipedia.org/wiki/Integrase%22%20%5Co%20%22Integrase), which splices the synthesized DNA into the host cell genome.
2. **Transcription inhibitors** Several antivirals are now being designed to block attachment of transcription factors to viral DNA.
3. **Translation/antisense inhibitors**: (**[fomivirsen](http://en.wikipedia.org/wiki/Fomivirsen%22%20%5Co%20%22Fomivirsen)** ) "antisense" molecules are segments of DNA or RNA that are designed as complementary molecule to critical sections of viral genomes.
4. **Protein processing inhibitors**: Interference with post translational modifications or with targeting of viral proteins in the cell is also possible.
5. **Protease inhibitors**: a [protease](http://en.wikipedia.org/wiki/Protease)  cuts viral protein chains apart so they can be assembled into their final configuration.
6. **Assembly inhibitors**: [Rifampicin](http://en.wikipedia.org/wiki/Rifampicin) acts at the assembly phase.
7. **Release inhibitors**: The final stage in the life cycle of a virus is the release of completed viruses from the host cell. [**zanamivir**](http://en.wikipedia.org/wiki/Zanamivir)(Relenza) and **[oseltamivir](http://en.wikipedia.org/wiki/Oseltamivir%22%20%5Co%20%22Oseltamivir)** (Tamiflu) that have been recently introduced to treat influenza prevent the release of viral particles by blocking a molecule named [neuraminidase](http://en.wikipedia.org/wiki/Neuraminidase) that is found on the surface of flu viruses.
8. **Immune system stimulation:**

A second category of tactics for fighting viruses involves encouraging the body's immune system to attack them, rather than attacking them directly. [Interferon](http://en.wikipedia.org/wiki/Interferons), which inhibit viral synthesis in infected cells.

**Antiviral for respiratory viral infection**

The viruses are influenza virus and respiratory syncetial virus (RSV). The influenza virus contains neuraminidase enzyme, so neuraminidase inhibitor treat influenza A and B.

1. **Neuraminidase inhibitor are:**
2. Oseltamivir: prevent releasing of virus from infected cell, it effective for A and B type, not affect the immunity for influenza vaccine.

Its prodrug, inactive orally so given by inhalation or nasal route, side effect of this drug is respiratory irritation.

1. **Inhibitor for viral uncoating:**
2. Amantidin and Rimantidin: this block viral membrane matrix protein which act as ion channel, this needed for fusion of viral protein with cell membrane to form endosome, also this block release of new virus.
* **Uses**:
1. Treatment and prevention of influenza A only.
2. Parkinsonism, because it ↑ dopamine and inhibit reuptake of dopamine at brain basal ganglion.
* Absorbed orally and cross BBB but not rimantidin.
* Both excreted by urine.
* **Side effect:**
1. DNA (dizziness, nystagmis, ataxia).
2. Convulsion.
3. Teratogenic.

Rimantidin cause fewer side effects (why?).

1. **Synthetic guanosine analogue:**
2. Ribavirin: it converted to ribavirin triphosphate → block GTP formation → block RNA polymerase.
* **Uses**:
1. Influenza virus.
2. RSV (respiratory syncetial virus).
3. Chronic hepatitis C.
* Absorbed orally at fatty media, not cross BBB, also can be given nasally.
* **Side effects:**
1. ↑ Bilirubin.
2. Teratogenic.
3. Hemolytic anaemia.
* **Antiviral for herpes viral infection:**

Herpes virus cause sore throat, encephalitis and genital infection

1. **Acyclovir:**
* Is a guanosin analogue, is monophosphorylated at viral thymidin kinase converted to di and triphosphated acyclovir → inhibit viral DNA polymerase → premature viral DNA chain termination, it less active for host enzyme.
* Given by any route, cross BBB and excreted by urine.
* **Side effects:**
1. Renal failure.
2. Thrombocytopenia.
* **Uses:**
1. Herpes viral infection:
2. Encephalitis (I.V.).
3. Meningitis (I.V.).
4. Shingle (topical).
5. Genital (topical).
6. **Cidofovir:**
* It nucleotide analogue, its phosphorylation **not** depend on viral enzyme, inhibit viral DNA synthesis.
* **Used** for cytomegalovirus (retinitis).
* **Side effects:**
1. Ocular hypotony.
2. Metabolic acidosis.
3. Neutropenia and nephrotoxicity.
4. **Fomivirsin:** block CMV mRNA, given intravitrealy, used for CMV iritis, vitritis.
5. **Foscarnet:**
* Its pyrophosphate derivative.
* Broad spectrum antiviral.
* It blocks viral DNA and RNA polymerase.
* Given I.V. because it less absorbed orally.
* **Indications:**
1. CMV retinitis.
2. Acyclovir – resistant herpes simplex virus.
3. Herpes zoster infection.
* **Side effects:**
1. Nephrotoxicity.
2. Because it chelating agent so it ↓ all ion lead to ↓ K+, ↓ Mg, ↓ Ca+, ↓ phosphate so lead to arrhythmia.
3. **Ganciclovir:** analogue for acyclovir, used only for CMV, it blocks DNA polymerase, given I.V., cross BBB.

Side effects: teratogenic, neutropenia.

1. **Vidarabine:** nucleoside analogue, converted by viral enzyme to vidarabine triphosphate which inhibits viral DNA polymerase.
* **Uses**:
1. Herpes simplex.
2. Herpes zoster.
3. CMV.

It only used topically for viral keratitis.

**Treatment of HIV**

The HIV contains two main enzymes, reverse transcriptase and protease enzyme.

So antiviral for **HIV classified into:**

1. Reverse transcriptase inhibitor (RTI).
2. Nucleoside reverse transcriptase inhibitor (NRTI).
3. Non- Nucleoside reverse transcriptase inhibitor (NNRTI).
4. Protease inhibitor.
5. Viral fusion inhibitor (**Enfuviritide**)
* This drug inhibits viral transmembrane glycoprotein (GP41) which responsible for viral binding to host cell.
* Given S.C. (subcutaneously), so cause erythma.
* **NRTI**: it phosphorylated within host cell lead to DNA inhibition and block DNA polymerase and termination of DNA elongation, the host mitochondrial DNA polymerase are susceptible to NRTI, so toxicity and fatal liver damage are the main side effects except for lamivudin which is **not** block host mitochondrial DNA polymerase.

The HIV reverse transcriptase enzyme form DNA from RNA and HIV mainly affect CD4 cell.

1. Zidovudine:
* Mainly drug for HIV, it decrease viral load and ↑CD4.
* It converted by host thymidine kinase to zidovudin triphosphate which inhibit reverse transcriptase inhibitor.
* Well absorbed orally, but ↓ with meal, cross BBB.
* Excreted by urine.
* **Side effects:**
1. Bone marrow depression.
2. Seizure.
* **Note**: Zidovudine metabolized by liver glucoronidase, so drug that ↓ activity of this enzyme potentiate the Zidovudine toxicity, these drugs are paracetamol, probenecid and cimetidin.
1. **Zalcitabine**:
* It inhibits RTE and DNA polymerase.
* Absorbed orally but affected by food.
* It causes peripheral neuropathy due to inhibition of host mitochondrial DNA polymerase.
* Pancreatitis.
1. **Lamivudin**: block RTE and DNA synthesis, it cause less side effect because it **not** block host mitochondrial DNA.
* **NNRTI**: non – cleoside reverse transcriptase inhibitor are highly selective non – competitive inhibitor of HIV RTE, so it block only HIV reverse transcriptase, **not** require activation by host enzyme, also cause less drug interaction and side effects.

**NNRTI drugs are:**

1. **Nevirapine:** absorbed orally, cross BBB, it reduce viral transmission during pregnancy.
* **Side effects:**
1. Steven – Johnson syndrome.
2. Fatal hepatotoxic.
3. Enzyme inducer so ↑ metabolism of other antiviral drugs.
4. **Delaviridine:**
* Well absorbed, not affected by food.
* Extensively metabolized and less excreted.
* Enzyme inhibitor, so ↓ metabolism of other drugs.
* **Protease inhibitors:**

All these drugs are reversible inhibitors of HIV protease which is responsible for cleavage of viral polyprotein into a number of essential enzymes (RTE, protease and integrase) and other structural proteins. The protease inhibitor exhibit 100 time selectivity for HIV enzyme than human protease. So inhibition of protease prevent viral maturation, most protease inhibitors poorly absorbed, all extensively metabolized so less excreted, all **not** cross BBB because these drugs require endothelial pump which are **not** present in brain capillaries.

* **Side effects:**
1. ↑ Cholesterol, ↑ triglyceride.
2. Buffalo hump.
3. Gynecomastia.
4. Enzyme inhibitor and drug interaction.

**Protease inhibitors are:**

1. **Saquinavir**: mainly excreted by bile, highly fatty meal ↑ its absorption.
2. **Ritonavor:** excreted by bile, its primary enzyme inhibitor so ↑ level of other protease inhibitors, so ritonavir regarded as **pharmacokinetic enhancer**.
3. **Nelfinavir:** non – protein protease inhibitor, not affected by food, its metabolite also have antiviral activity.
4. **Atazanavir**: excreted by bile, it inhibitor for glucoronyl transferase so lead to jaundice, also it ↓ the hyperlipidemia.

## Protease inhibitors also used A combination of ritonavir and lopinavir was found to have some effectiveness against [Giardia](http://en.wikipedia.org/wiki/Giardia%22%20%5Co%20%22Giardia) infection. The drugs saquinavir, ritonavir, and lopinavir have been found to have anti-malarial properties. A cysteine protease inhibitor drug was found to cure [Chagas disease](http://en.wikipedia.org/wiki/Chagas_disease%22%20%5Co%20%22Chagas%20disease) in mice. Researchers are investigating whether protease inhibitors could possibly be used to treat cancer. For example, nelfinavir and atazanavir are able to kill tumor cells in culture . This effect has not yet been examined in humans; but studies in laboratory mice have shown that nelfinavir is able to suppress the growth of [Multiple Myeloma](http://en.wikipedia.org/wiki/Multiple_Myeloma).